REMARKS

Claim 1 has been amended to incorporate the limitations of claim 2, and claim 2 has been canceled.

Claim 4 has been amended to change its dependency from claim 2 to claim 1.

Claims 17 and 19 have been amended to remove the term “aqueous.”

Claim 8 has been amended to correct a typographical error.

These amendments are supported by the original claims, as well as by pages 7 through 11 of the specification. Regarding to the amendment to claims 17 and 19, see particularly page 7, lines 12-13, and page 9, lines 13-20.

Upon entry of the Amendment, claims 1 and 3-22 will be pending, of which claims 9-22 are withdrawn from consideration. No new matter has been added. Entry of this Amendment is respectfully requested.

Election/Restriction - Request for Rejoinder

The Examiner acknowledges Applicants’ election and species selection with traverse of claims 1-8 of Group I; however, the restriction of the method claims has remained in effect. The restriction requirement is still deemed proper and has been made final.

Applicants have amended independent withdrawn claim 17 to depend from claim 1 in order to be eligible for rejoinder in accordance with MPEP §821.04(b). Method claim 9 already depends from claim 1 and is thus eligible for rejoinder. Applicants respectfully request rejoinder of non-elected method claims 9-22 upon allowance of claim 1.

Response to Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Takada et al. (U.S. Patent 6,117,455) in view of Baker et al. (U.S. Patent 5,399,558).

The Examiner asserts that Takada discloses 1 nm - 10 μm particles comprising up to 90% drug and a polymer. Further, the Examiner states that Takada discloses anti-tuberculosis agents, specifically Isoniazid.

The Examiner states that Baker discloses that Isoniazid and Rifabutin are known in the art to treat tuberculosis, and that suitable amounts are taught in the Physicians' Desk Reference.

The Examiner asserts that the addition of Rifabutin disclosed by Baker to the composition taught by Takada to achieve a beneficial effect of a second anti-tuberculosis agent would have been obvious to one of ordinary skill. Further, the Examiner asserts that the determination of the particular ratio of drug to polymer and drug to drug may be achieved by routine experimentation.

Applicants respectfully traverse the rejection for the following reasons.

1. The Claimed Combination Of Two Anti-tuberculosis Drugs Is Non-Obvious In View Of The Cited References

Respectfully, it is believed that there is insufficient motivation to combine the teachings of Takada et al. with Baker et al.

The Examiner states that "it would have been obvious to one of ordinary skill to add rifabutin to the composition Takada et al for beneficial effect of a second anti-tuberculosis agent in view of Baker et al."

However, the MPEP at Section 2143.01 states:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Takada and Baker do not teach the beneficial effects of the combination of two anti-tuberculosis drugs, especially Rifabutin and Isoniazid in a critical ratio of 1:2 to 2:1 along with a polymer in microparticles. Moreover, it is known in the art that Rifabutin and Isoniazid normally form an adduct which results in reduced bio-availability and efficacy of these drugs, thus preventing the drug combination from being used for the management of pulmonary tuberculosis (Sharma R., et al., *Inhalable microparticles containing drug combinations to target alveolar macrophages for treatment of pulmonary tuberculosis*. Pharm Res. 2001 Oct;18(10):1405-10). Similarly, Rifampicin type anti-tubercular drugs which do not contain a piperazine moiety can be attacked by Isoniazid leading to the formation of an adduct. Thus, because the art at the time of invention teaches away from the present invention, one of skill in the art could not have been motivated to combine two anti-tuberculosis drugs.

Further, the inventive step of the present application is achieved by incorporating two drugs of differing solubility within the same microparticle. The present application discloses having a homogeneous solution conformable for spray drying from mixing a methanolic solution of Isoniazid with a solution of polylactic acid and Rifabutin in dicholoromethane (specification, page 9, lines 13-15). However, it is known in the art that methanol is used as a non-solvent for polylactic acid in order to prepare micro- or nano-particles from dichloromethane (Fessi, H.; Devissaguet, JP; Puisieux, F.; Thies, C. French Patent 2 608 988, 1986; Peltonen L, Koistinen P, Karjalainen M, Hakkinen A, Hirvonen J. *The Effect of Cosolvents on the Formulation of Nanoparticles From Low-Molecular-Weight Poly(L)lactide*. AAPS PharmSciTech. 2002; 3(4): article 32). The present application discloses a narrow range of solvent ratios adequate to dissolve the required amounts of the components without precipitating polylactic acid from solution (specification, page 7, lines 9-17). Thus, in view of what was known in the art at the time of the invention, a skilled artisan could not have reasonably expected to successfully incorporate two anti-tuberculosis drugs into microparticles.

2. The Claimed Ratios Of Drug(s) to Polymer and Of Drug to Drug Are Critical

With regard to the Examiner's position that the determination of optimum ratios may be achieved by routine experimentation, Applicants respectfully point to the unexpected results obtained using the claimed ratios. The ratios of the drugs and the polymer provide for an optimal controllable rate of release of drugs, a sighting action on the lungs and on microbacteria-infected macrophages with no side effects. Higher concentrations of polymers reduce the required dosage of the active component, the bioavailability of the preparation, and the efficiency of treatment of pulmonary tuberculosis. Thus, the claimed ratio of preparations/polymer allows for the extended action of the drugs in the lungs, for providing greater bioavailability of the preparations, and for reduction of treatment costs due to improved efficacy and reduced course of treatment.

As described on page 11 of the specification, and in Figures 1 and 2, the treatment of *M. tuberculosis* infected animals by an inhalation route using microparticles in combination with an oral administration (using half the dose) resulted in a faster clearance of tubercle bacilli from the organs. For example, see Figures 1 and 2, showing that the lungs and spleen were found to be free of infection in all infected mice treated by inhalation in combination with half the oral dose of pure drugs, as compared to those treated by oral administration with either combination or pure drug or alone. These effects are not taught or suggested by the cited references, and have not been fairly considered by the Examiner.

3. The Cited References Do Not Teach Or Suggest That The Inhalable Microparticle Composition Comprising The Two Anti-Tuberculosis Drugs And A Polymer Has a Diameter In The Range Of 1-15 μm, Preferably Less Than 10 μm

Takada et al. teach a pharmaceutical agent having a particle size from 1 nm - 10 μm and a polymer. Further, efforts have been made to obtain the drug in the particle size of 1 nm - 10 μm by pulverizing it to microparticles by conventional methods such as jet mill, atomization, or ball mill methods (Takada et al., at column 11, lines 43-48). In the present application, Applicants used the drugs as such in powder form for making a composition of the drugs and polymer in inhalable microparticles having a diameter in the range of 1-15μm, preferably less than 10 μm. Thus, Takada et al. do not teach the composition comprising the drugs and the copolymer having a particle size from 1-15 μm, preferably less than 10 μm.

Given the reasons above, the Examiner cannot make a *prima facie* case for obviousness and, even if such case could be made, these reasons clearly shift the burden of proof back onto the Examiner.

Thus, claims 1-8 should be held patentable.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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